The association between sleep duration and cancer-specific mortality: a systematic review and meta-analysis

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Abstract:

Purpose: In this systematic review and meta-analysis, we aimed to estimate cancer-specific mortality and all-cause mortality among cancer survivors associated with both short (typically 5 or 6 h/night) and long (typically 9 or 10 h/night) sleep duration (versus recommendations), separately by sex, cancer site, and sampling frame. **Methods:** We completed a systematic literature search in five databases and captured relevant literature published through December 2018. Two reviewers independently screened 9,823 records and 32 studies were included representing over 73,000 deaths in cancer survivors. Estimates for short and long sleep duration compared to 'recommended' were pooled using random-effects models. **Results:** Pooled hazards ratios for short and long sleep duration for all-cancer-specific mortality were 1.03 (95% CI 1.00–1.06) and 1.09 (95% CI 1.04–1.13), respectively. In subgroup analyses by cancer site, statistically significant increased risks were found for both short and long sleep durations for lung cancer-specific mortality. These associations were maintained when stratified by sex and sampling frame. There were no statistically significant associations found between either short or long sleep duration and breast, colorectal, ovarian, or prostate cancer-specific mortality. Statistically significant increases in all-cause mortality were observed with long sleep duration in breast cancer survivors (1.38; 95% CI 1.16–1.64) with no significant associations found for colorectal or liver/pancreatic cancers. **Conclusions:** We observed that long sleep duration increases cancer-specific mortality for all-cancers and lung cancers, while all-cause mortality is increased for breast cancer survivors. Limitations were found within the existing literature that need to be addressed in future studies in order to improve the understanding regarding the exact magnitude of the effect between sleep duration and site-specific mortality.

Keywords: Cancer survivorship | Meta-analysis | Sleep duration | Mortality

Article:

Introduction

Evidence suggests that both short and long sleep durations are associated with a plethora of adverse outcomes [1, 2] including all-cause mortality [3,4,5], Type II diabetes [6], cardiovascular events and disease outcomes [4, 7, 8], cancer risk [9], and cancer-specific mortality [10]. Recent findings suggest that sleep is disturbed in cancer patients and survivors [11,12,13,14] and that sleep disruption in cancer patients and survivors can lead to increased risk of morbidity, mortality, and poor quality of life [12]. Inconsistent results have been found in observational studies regarding the association between sleep duration and cancer mortality. Some studies have observed a U-shaped association [15], while other studies have observed associations for long but not short sleep durations [16, 17] or no association [18]. These inconsistencies warrant further investigation of the effects of sleep duration on cancer-specific mortality, given the growing amount of evidence that remains inconsistent regarding the nature of these associations. Additionally, with more published evidence that has provided site- and sex-specific estimates, it is important to investigate whether or not typical sleep duration is associated with mortality for individual cancer sites rather than all-cancer sites combined, and if sex acts as an effect modifier with different magnitudes of association found in men and women. The rationale for providing these separate estimates is that each cancer site has a different etiology and mortality rate. While precise biological mechanisms remain to be elucidated, inflammatory processes [19,20,21], oxidative stress [22], and suppressed melatonin [23] have been proposed. Though sleep disruption does not necessarily indicate specifically short or long duration sleepers, it has been suggested that sleep disruption can lead to systemic inflammation, which has been linked to tumor progression, cancer aggressiveness, and recurrence, which may also be mechanisms linking sleep duration to these outcomes [12, 24, 25].

Two meta-analyses related to sleep duration and cancer mortality have been conducted to date [5, 10]. The first found an association for long, but not short, sleep duration on the risk of cancer mortality, though it was limited to three studies and may have lacked statistical power to find an effect [5]. Similarly, the second meta-analysis of prospective studies investigating the relation between cancer mortality and sleep duration found that long sleep duration ($\geq$ 9–10 h; RR = 1.11, 95% CI 1.05–1.19), but not short sleep duration ($\leq$ 5–6 h; RR = 1.05, 95% CI 0.99–1.11), was associated with total cancer mortality [10]. Since 2015, 15 papers from large prospective studies have been published on the topic, including six conducted within cohorts of cancer survivors. Moreover, neither of the reviews mentioned investigated the effect of sleep duration on all-cause mortality or were able to investigate cancer-specific mortality by cancer site.

To clarify the relation between short and long sleep duration on cancer mortality, we conducted a systematic review and meta-analysis of prospective observational studies. The aim of this meta-analysis was to investigate the risk of all-cause mortality in cancer survivors and cancer-specific mortality for both long (typically > 8–10 h) and short (typically < 5–7 h) sleep duration compared to reference sleep duration ranges, typically defined as 7–8 h per night for older adults [26]. Secondary aims were to explore subgroup analyses investigating these relations by both sex and cancer site, as well as exploring potential differences based on study sampling frames.

Methods

The systematic review protocol was registered in PROSPERO (registration number: CRD42017078468).

Literature search strategy

Five databases were searched through 31 October 2017 including PubMed, MEDLINE OVID, EMBASE, CINAHL, and PsycINFO using the following search strategy: ((sleep* OR sleep/OR "sleep duration" OR "sleep deprivation" OR "sleep time") AND (cancer OR cancer/OR neoplasm OR carcinoma OR tumour OR tumor) AND (mortality OR survival OR death OR recurrence OR progression OR outcome* OR fatal)). Keywords (including any associated synonyms) along with medical subject headings for cancer, sleep, and mortality were included in the search. There were no restrictions by type or site of cancer, language, date, or geographical region. Moreover, reference lists of relevant review articles and all included studies were searched manually to identify any additional studies for inclusion, and reverse citation searches were conducted for all included studies. Additionally, e-alert notifications were established for PubMed to capture additional articles through 31 December 2018.

Selection criteria

The following predetermined inclusion criteria were applied: (i) an observational study design; (ii) short or long sleep duration as the exposure of interest; (iii) all-cause or cancer-specific mortality as the outcome of interest; (iv) night time sleep duration, not restricted to those with sleep-related disorders or insomnia; and (v) risk estimates (risk ratios (RRs)/hazards ratios (HRs)) with corresponding 95% confidence intervals (95% CIs). The PRISMA flow diagram documenting all phases of literature search is provided in Fig. 1. In brief, all duplicates were removed and titles and abstracts were screened in duplicate by two independent reviewers (C.R.S and T.R.H) and excluded if they were (1) not on topic; or (2) not original research (i.e., reviews pertaining to sleep and cancer). The two reviewers then independently screened the full-text articles of abstracts identified in the first stage of review. Articles were excluded if they were (1) not on topic; (2) not original article (i.e., conference abstract, review, commentary); (3) results were not presented and authors could not be reached to obtain said results; or (4) the source population used in the study had been previously published (i.e., duplicate populations). Discrepancies were resolved by discussion and confirmed by a third author (J.M).

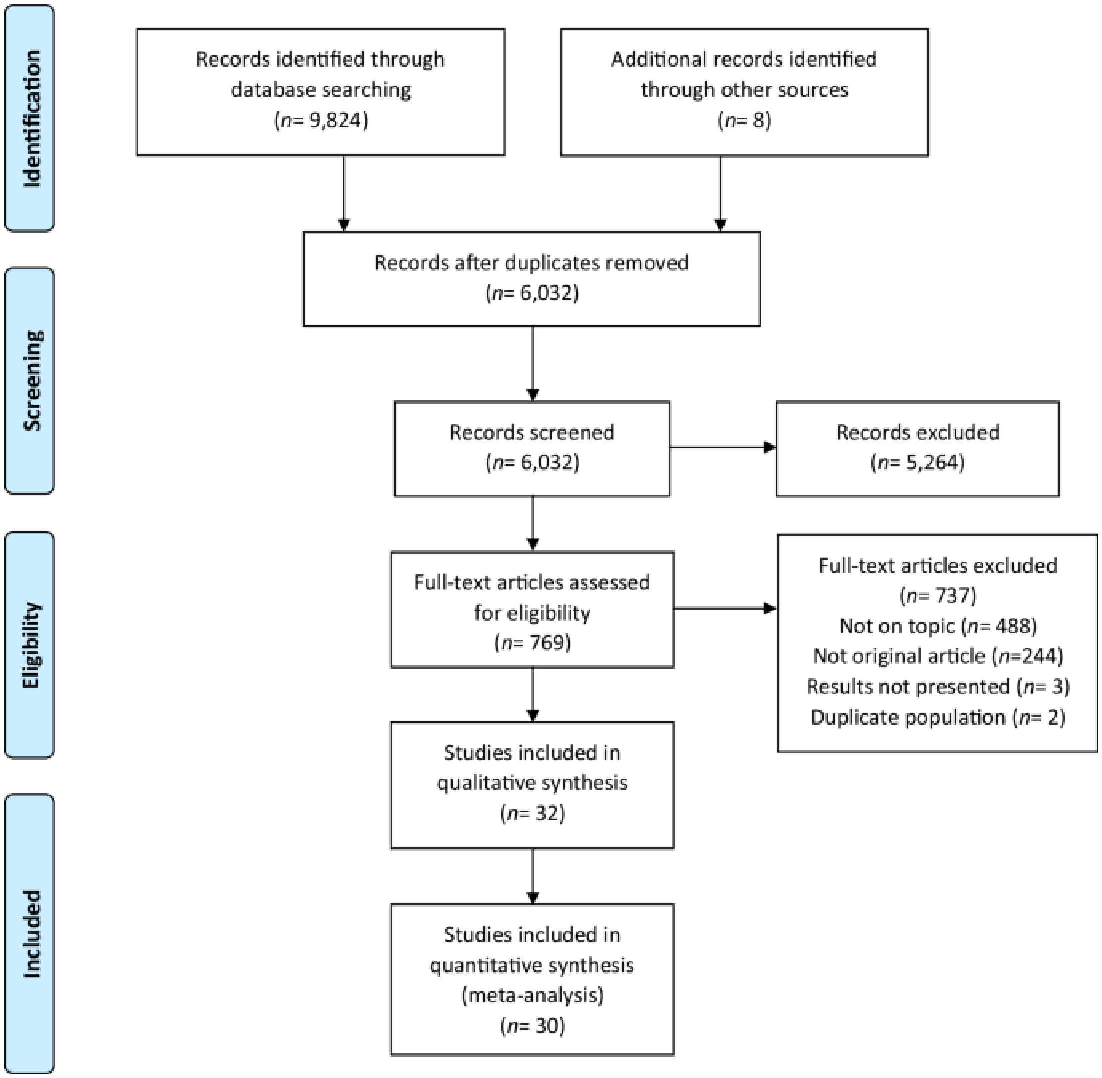


Fig. 1. PRISMA flowchart through all phases of the systematic literature search and review

Data extraction

A data-extraction form was created specifically for this review and was pilot tested by co-authors (T.R.H and C.R.S). Extraction was conducted independently (C.R.S) and verified by another reviewer (T.R.H). The form was used to extract the following information from each study: first author's last name, year of publication, study country, study/cohort name, recruitment dates, follow-up duration, study population age, distribution by sex, number of participants and number of cancer deaths, participant source, and mortality ascertainment. Additionally, information was extracted on data capture methods and definitions of sleep duration, and sub-groups based on age, sex, or cancer site. Statistical model covariate adjustment factors and corresponding risk estimates HRs or RRs and 95% CIs for shortest and longest levels of sleep duration with all-cause and cancer-specific mortality associated were extracted. We contacted five authors by e-mail up to two times to request results where estimates were not presented. Four authors replied, and three were able to provide additional information required for inclusion in our review.

Study quality assessment

Study quality was assessed using the Newcastle–Ottawa Scale for observational cohort studies [27]. This scale includes three domains: selection, comparability, and outcome. The elements on this scale include (i) assessment of the representativeness of the sample selection (cases and controls); (ii) ascertainment method of the exposure; (iii) demonstration that the outcome was not present at study start; (iv) important control of known covariates compared to other similar studies; (v) assessment method of the outcome; (vi) sufficiency of length of follow-up; and (vii) adequacy of follow-up (attrition/loss-to-follow-up). A full description of each item is presented in Online Resource 1.

Statistical analysis

Risk estimates were obtained from the most fully adjusted multivariate models within each of the studies. Sex and cancer site-specific estimates were considered independent reports in studies that reported specific subgroup results and these estimates were extracted as well as those for the overall study population. The pooled HRs with 95% CIs were obtained using a random-effects model since it was assumed that the included studies will differ because of random error and between study variability [28]. Potential sources of heterogeneity by sex and study sampling frame (i.e., studies with reported healthy cohorts at baseline versus studies incorporating individuals with pre-existing cancer diagnoses) were explored within cancer sites using subgroup and meta-regression analyses within cancer-specific mortality where appropriate. We estimated and quantified heterogeneity using the Cochran Q test and I^2 statistics [29]. The following cut-off points were used for the I^2 statistic: < 25% (indicating little or no heterogeneity), 25–75% (moderate heterogeneity), and > 75% (high heterogeneity) [30]. The Begg's rank correlation [31] and Egger's linear regression [32] tests were used to investigate any potential publication bias. All statistical analyses were performed using STATA software, version 14.2 (STATA Corp., College Station, TX, USA). All p-values were two-sided, and the level of significance was considered $\alpha < 0.05$.

Results

Search results and study characteristics

We identified 9,824 records from our database search, four from searching reference lists and four from updated e-alert notifications (Fig. 1). After removing duplicates, 6,030 titles/abstracts remained that were screened by two independent reviewers. Seven hundred and sixty-seven records were eligible for full-text screening, that resulted in 99.74% agreement on inclusion/exclusion ($\kappa = 0.96$) achieved after independent review. A total of 32 records qualified for final inclusion in this systematic review, and 30 records were included in the meta-analysis.

Table 1. Characteristics of the included studies that evaluated the association between sleep duration and all-cause and cancer-specific mortality

First author, year of publication	Name of study, country	Population age range or mean age	Study duration	No. of participants	Cancer deaths	Outcome, sex	Sleep assessment timing	Long sleep duration	Short sleep duration	Reference sleep duration	Adjusted covariates
Mallon, 2002 [42]	NR, Sweden	45–65 years	12 years	1,870	83	Cancer-specific male (all), female (all)[a]	Unclear	> 8 h	< 6 h	6–8 h	Age
Amagai, 2004 [33]	Jichi Medical School Cohort Study, Japan	30–69 years	9 years	11,325	201	Cancer-specific male (all), female (all)	Pre-diagnosis	> 9 h	< 5.9 h	7–7.9 h	Age, BMI, systolic blood pressure, total cholesterol, smoking, alcohol drinking, education, and marital status
Patel, 2004 [45]	Nurses' Health Study (NHS), USA	30–55 years	14 years	82,969	2,642	Cancer-specific female (all)[a]	Unclear	> 9 h	≤ 5 h	7 h	Age, BMI, smoking, alcohol drinking, physical activity, depression, snoring, CVD, hypertension, diabetes, shift-working history
Lan, 2007 [41]	Survey of Health and Living Status of the Elderly, Taiwan	≥ 64 years	10 years	3,079	278	Cancer-specific male (all), female (all)	Unclear	≥ 10 h	< 7 h	7–7.9 h	Age, BMI, marital status, monthly income, smoking, alcohol drinking, exercise, disease history, and depression
Suzuki, 2007 [48]	The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC), Japan	40–79 years	15 years	109,778	6,219	Cancer-specific male (all) and female (all), and cancer site by sex	Unclear	> 9 h	< 7 h	7–8 h	Age and area of study
Stone, 2009 [55]	Study of Osteoporotic Fractures (SOF) prospective cohort study, USA	≥ 69 years	8 years	8,101	423	Cancer-specific female (all)	Unclear	≥ 10 h	NE	8 to < 9 h	Age, BMI, history of various medical conditions (including chronic diseases and cancer), walks for exercise, alcohol use, smoking status, depression, cognitive impairment, estrogen use, and benzodiazepine use
Kakizki, 2013 [39]	Ohsaki National Health Insurance (NHI) Cohort Study, Japan	40–79 years	13 years	51,253	2,764	Cancer-specific overall	Unclear	≥ 10 h	≤ 6 h	7 h	Age, sex, BMI, total caloric intake, marital status, education, job status, myocardial infarction, stroke, hypertension, diabetes mellitus, smoking, alcohol drinking, time spent walking, perceived mental stress, self-rated health, and physical function
Kim, 2013 [40]	The Multiethnic Cohort (MEC) Study, USA	45–75 years	14 years	135,685	6,772	Cancer-specific male (all), female (all)	Pre-diagnosis	≥ 9 h	≤ 5 h	7 h	5-year age groups at cohort entry, ethnicity, education, marital status, history of hypertension or diabetes at enrollment, alcohol consumption, energy intake, body mass index, physical activity, hours spent daily watching television, and smoking history
Yeo, 2013 [51]	Korean Multi-center Cancer Cohort (KMCC) Study, Korea	≥ 20 years	17 years	13,164	526	Cancer-specific overall, male (all),	Unclear	≥ 10 h	≤ 5 h	7 h	Age, BMI, education, smoking, alcohol drinking, hypertension, type 2 diabetes, CVD, and metabolic syndrome

First author, year of publication	Name of study, country	Population age range or mean age	Study duration	No. of participants	Cancer deaths	Outcome, sex	Sleep assessment timing	Long sleep duration	Short sleep duration	Reference sleep duration	Adjusted covariates
						female (all), < 60 y (all), ≥ 60 y (all)					
Bellavia, 2014 [35]	Cohort of Swedish Men and the Swedish Mammography Cohort, Sweden	45–83 years	15 years	70,973	3,508	Cancer-specific overall	Pre-diagnosis	> 8 h	< 6 h	6.6–7.4 h	Age at baseline, sex, BMI, smoking status and pack-years of smoking, alcohol consumption, and educational level, total physical activity
Carter, 2014 [37]	The Cancer Prevention Study-II, USA	50.3 years	28 years	161,004	1,289	Cancer-specific female (ovarian)[a]	Pre-diagnosis	9–12 h	3–5 h	7 h	Oral contraceptive use, age at menarche and menopause, tubal ligation, parity, postmenopausal estrogen use, race, family history of breast/ovarian cancers, exercise, BMI, and height
Gapstur, 2014 [38]	The Cancer Prevention Study-II, USA	≥ 29 years	28 years	305,057	4,974	Cancer-specific male (prostate)[a]	Pre-diagnosis	10–12 h	3–5 h	7 h	Age, race, education, BMI, smoking status, family history of prostate cancer, and painful/frequent urination
Palesh, 2014 [59]	NR, USA	≥ 45 years	10 years	97	58	All-cause female (breast)	Post-diagnosis	8–9 h	< 7 h	7–8 h	Age, estrogen receptor status, treatment, dominant site of metastatic disease spread, depression, and cortisol levels
Cancer cohort											
Rod, 2014 [46]	Whitehall II Cohort Study, UK	35–55 years	25 years	9,098	374	Cancer-specific male (all), female (all)	Pre-diagnosis	> 9 h	≤ 6 h	7–8 h	Age, employment grade, ethnicity, and marital status
Xiao, 2014 [49]	NIH-AARP Diet and Health Study, USA	51–72 years	16 years	239,896	16,644	Cancer-specific overall, BMI-specific[a]	Pre-diagnosis	≥ 9 h	< 5 h	7–8 h	Age, sex, BMI, ethnicity, marital status, education, self-reported health, smoking, alcohol consumption, moderate-vigorous physical activity, and TV Viewing. Excluded deaths occurring within 3 years after baseline
Cai, 2015 [36]	Shanghai Women's Health Study and Shanghai Men's Health Study, China	40–79 years	13 years	113,138	NR	Cancer-specific overall, male (all), female (all), cancer site	Unclear	≥ 10 h	< 6 h	7 h	Education, income, smoking, alcohol consumption, tea consumption, comorbidity score, history of night-shift work, participation in regular exercise, body mass index, and waist-to-hip ratio
Markt, 2015 [43]	The National March Cohort (NMC), Sweden	51.5 years	13 years	12,976	118	Cancer-specific male (prostate)	Pre-diagnosis	≥ 9 h	≤ 5 h	8 h	BMI, employment status, snoring, smoking, alcohol use, depressive symptoms, physical activity, coffee intake, multivitamin use, and diabetes
Bai, 2016 [34]	Dongfeng–Tongji Cohort Study, China	63.6 years	5 years	25,377	379	Cancer-specific overall, male (all), female (all)	Pre-diagnosis	≥ 10 h	< 7 h	7–8 h	Age, BMI, family history of cancer, alcohol drinking and smoking status, and pack-year
Dickerman, 2016 [56]	The Older Finnish Twin Cohort, Finland	40 years	31 years	11,370	110	Cancer-specific male (prostate)	Pre-diagnosis	> 8 h	NE	< 7 h	Age, education, BMI, physical activity, social class, smoking status, alcohol use, snoring, and zygosity

First author, year of publication	Name of study, country	Population age range or mean age	Study duration	No. of participants	Cancer deaths	Outcome, sex	Sleep assessment timing	Long sleep duration	Short sleep duration	Reference sleep duration	Adjusted covariates
Markt, 2016 [44]	Health Professionals Follow-Up Study, USA	40–75 years	23 years	32,141	563	Cancer-specific male (prostate)[a]	Pre-diagnosis	> 10 h	≤ 5 h	8 h	Age, race, vigorous activity level, smoking, diabetes, family history of prostate cancer, snoring status, multivitamin use, energy intake, history of PSA testing, beta-blocker use, marital status, coffee intake, alcohol intake, and number of urinations per night
Phipps, 2016 [18] Cancer cohort	The Women's Health Initiative (WHI), USA	50–79	21 years	21,230	4,482	Cancer-specific female (all), cancer site	Pre-diagnosis	≥ 9 h	≤ 5 h	7–8 h	Age at enrollment, study arm, cancer site, marital status, household income, smoking history, recreational physical activity, and lag time between baseline data collection and cancer diagnosis
Smagula, 2016 [47]	The Osteoporotic Fractures in Men Sleep Study, USA	> 65	7.4 years (average)	2,531	171	Cancer-specific male (all)	Unclear	> 8 h	< 5 h	5–8 h	Age, study site, race, body mass index, probable depression, cognition, alcohol use, education, smoking status, caffeine use, physical activity, chronic disease, self-reported health and medication use, and number of high inflammatory markers
Akerstedt 2017 [54]	The Swedish National March, Sweden	≥ 18	13 years	39,191	1,645	Cancer-specific overall	Unclear	≥ 8 h	≤ 5 h	7 h	Age, sex, BMI, smoking status, alcohol consumption, educational level, physical activity, and major disease
Collins, 2017 [60] Cancer cohort	NR, USA	≥ 21 years	5 years	292	NR	All-cause hepatobiliary/ pancreatic	Post-diagnosis	≥ 9 h	< 6.5 h	7.5 h	Age, gender, education, diagnosis, vascular invasion, depression, and snoring
Marinac, 2017 [16] Cancer cohort	The Women's Healthy Eating and Living (WHEL) Study, USA	18–70 years	15 years	3,047	446	Cancer-specific and all-cause female, breast	Post-diagnosis	≥ 9 h	≤ 6 h	7–8 h	Age, stage, grade, body mass index, number of comorbidities, race/ethnicity, intervention group, and study site
Ratjen, 2017 [58] Cancer cohort	NR, Germany	69 years (median)	12 years	1,376	200	All-cause colorectal	Post-diagnosis	≥ 9 h	≤ 6 h	7–8 h	Sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, alcohol intake, (time × age), (time × BMI), and (time × metastases)
Trudel-Fitzgerald, 2017 [17] Cancer cohort	Nurses' Health Study (NHS), USA	30–55 years	26 years	3,682	412	Cancer-specific and all-cause female (breast)	Post-diagnosis	≥ 9 h	≤ 6 h	8 h	Year of diagnosis, age at diagnosis, time since diagnosis, cancer stage, surgery, chemotherapy, radiation therapy, hormone therapy, prevalent diabetes or heart disease, missing indicators for oncologic treatments, age, marital status, education level, income, OC use, number of pregnancies, family history of breast cancer, menopausal status, PMH use, BMI, alcohol intake

First author, year of publication	Name of study, country	Population age range or mean age	Study duration	No. of participants	Cancer deaths	Outcome, sex	Sleep assessment timing	Long sleep duration	Short sleep duration	Reference sleep duration	Adjusted covariates
Wong, 2017 [15]	The Xuanwei Cohort Study of farmers, China	> 21 years	19 years	42,422	4,829	Cancer-specific male and female age-specific (lung cancer)	Pre-diagnosis	≥ 10 h	≤ 7 h	8 h	Average hours spent performing indoor activities in the same age period as sleep, type of respondent, other work besides farming, educational attainment, duration of smoking, ever active smoking, ethnicity, average number of rooms and people in residences from 1976 to 1992, fuel type used in first residence, installation of a chimney for ventilation, family history of any cancer, average tons of fuel/coal used from 1976 to 1992, ever employment as a miner, age in 1976, history of respiratory comorbidities
Xiao, 2017 [50] Cancer cohort	NIH-AARP Diet and Health Study, USA	50–71 years	16 years	4,869	1,250	All-cause (colorectal)	Pre-diagnosis	> 9 h	< 5 h	7–8 h	Age at diagnosis, sex, cancer site, tumor stage, tumor grade, surgery, chemotherapy, radiation, education, smoking, TV viewing, MVPA, BMI, self-reported health, history of heart disease, history of stroke, history of diabetes and napping
Kabat, 2018 [53]	The Women's Health Initiative (WHI), USA	50–79 years	23 years	158,203	10,156	Cancer-specific female (all)	Pre-diagnosis	≥ 10 h	≤ 5 h	7 h	Age, smoking status, pack-years of smoking, alcohol intake, hormone therapy, body mass index, red meat intake, physical activity, marital status, depression, history of diabetes, history of cancer, history of cardiovascular disease, systolic blood pressure, health status, educational level, ethnicity, and study participation
Khan, 2018 [57]	The Kuopio Ischemic Heart Disease Study, Finland	42–61 years	30 years	1,734	229	Cancer-specific male (all)	Pre-diagnosis	> 10.2 h	NE	< 8	Age, diabetes, smoking, alcohol use, BMI, systolic blood pressure, serum creatinine and serum LDL-c, physical activity, serum C-reactive protein
Soh, 2018 [52]	The Singapore Chinese Health Study, Singapore	45–74 years	22 years	39,523	1,989	Cancer-specific overall	Unclear	≥ 9 h	≤ 5 h	7 h	Age, year of recruitment, gender, dialect group, physical activity, level of education, smoking status, alcohol intake, body mass index, history of hypertension, ischemic heart disease, stroke, diabetes, and cancer

NR not reported, *NE* not evaluated, *BMI* body mass index, *CVD* cardiovascular disease, *OC* oral contraception, *PMH* postmenopausal hormone

[a]Indicates use of RR rather than HR

Study characteristics for the 32 included studies are presented in Table 1. Ultimately, 26 studies reported estimates for short sleep duration and cancer-specific mortality [15,16,17,18, 33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54], 29 studies reported on long sleep duration and cancer-specific mortality [15,16,17,18, 33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57], and 6 studies on short and long sleep duration for all-cause mortality within cancer survivors [16, 17, 50, 58,59,60]. Of the 32 included studies, 15 were conducted in the United States [16,17,18, 37, 38, 40, 44, 45, 47, 49, 50, 53, 55, 59, 60], nine in Asia (China, Japan, Korea, Singapore, and Taiwan) [15, 33, 34, 36, 39, 41, 48, 51, 52], and eight in Europe (Finland, Germany, Sweden, and the United Kingdom) [35, 42, 43, 46, 54, 56,57,58].

Table S1 summarizes the findings of the study quality assessment according to the Newcastle–Ottawa Scale for observational studies. In general, the 32 studies included were of high quality. None of the 32 studies had low-quality ratings for the selection criteria including the representativeness of the exposed cohort, ascertainment of the exposure, and demonstration that the outcome was not present at start of study. Sleep duration was most commonly obtained via self-reported questionnaires, with only six studies receiving high-quality scores from utilizing objective measurements such as actigraphy. With respect to comparability, three of the 32 studies were given poor quality ratings because it was unclear whether or not age had been adequately controlled for in the analysis. Additionally, two different studies were given poor quality ratings because they failed to control for other important factors, besides age, (e.g., sex, education, body mass index, physical activity treatment details, smoking history). All studies received high-quality ratings with respect to two of the three outcome criteria (assessment of the outcome and sufficient follow-up time); however, information on attrition and loss-to-follow-up was lacking in a large number of these studies and therefore, 16 of the 32 received poor quality ratings with respect to this criterion.

Short sleep duration and mortality

The forest plot for the association between short sleep duration and all-cancer-specific mortality is shown in Fig. 2. For all-cancer-specific mortality, there was a non-statistically significant 3% increased risk for individuals reporting the lowest sleep duration (typically 5–6 h/night) compared to reference ranges (HR = 1.03; 95% CI 1.00–1.06), with negligible heterogeneity ($I^2 = 0.8\%$). Results were similar across differences in sampling frames (HR = 1.03 vs. 1.04).

Results for subgroup analyses according to cancer sites (all-cancer, lung, colorectal, breast, and prostate) and sex (male or female) are presented in Table 2. Within sex sub-groups for all-cancer, neither males nor females had statistically significant associations with cancer-specific mortality. In studies that investigated cancer-specific mortality for colorectal, breast, ovarian, or prostate cancers, there were non-statistically significant associations with low-moderate heterogeneity present (I^2 ranging from 0.0 to 57.1%). Lung cancer was the only cancer site found to be associated with a statistically significant elevated risk of mortality (21.0%) in short duration sleepers (HR = 1.21; 95% CI 1.10–1.33). The statistically significant increased risk of lung cancer-specific mortality was maintained in stratified analyses by sex, and though estimates were not statistically different, males had a slightly higher magnitude of risk compared to females (HR = 1.24 vs. 1.17).

Table 2. Results of subgroup meta-analysis for the association between short and long sleep duration with cancer-specific and all-cause mortality

Subgroup	Short sleep duration					Long sleep duration				
	No. of studies	No. of estimates[a]	Pooled HR estimate	95% CI	I^2 (%)	No. of studies	No. of estimates[a]	Pooled HR estimate	95% CI	I^2 (%)
Cancer-specific mortality										
Cancer site										
All-cancers	18	24	1.03	1.00–1.06	0.8	20	26	1.09	1.04–1.13	5.4
Cancer-free baseline	11	16	1.03	0.98–1.07	10.6	12	17	1.06	1.02–1.11	0.0
Other[b]	7	8	1.04	0.99–1.11	0.0	8	9	1.18	1.05–1.33	32.5
Female	12	12	1.03	0.98–1.08	0.0	13	13	1.13	1.03–1.23	25.9
Male	10	10	1.01	0.92–1.11	24.0	11	11	1.10	1.05–1.16	7.8
Lung	4	16	1.21	1.10–1.33	58.4	4	16	1.65	1.36–2.00	84.5
Cancer-free baseline	3	15	1.20	1.09–1.33	61.2	3	15	1.65	1.35–2.03	85.5
Other[b]	1	1	1.23	0.91–1.67	–	1	1	1.58	1.06–2.35	–
Female	4	9	1.17	1.02–1.35	56.6	4	9	1.51	1.18–1.93	73.2
Male	3	8	1.24	1.09–1.43	60.8	3	8	1.79	1.32–2.43	89.6
Colorectal	4	7	1.03	0.86–1.22	28.0	4	7	1.12	0.91–1.37	30.4
Cancer-free baseline	3	6	1.00	0.82–1.23	37.1	3	6	1.04	0.88–1.24	0.0
Other[b]	1	1	1.18	0.75–1.85	–	1	1	2.17	1.24–3.80	–
Female	3	4	0.97	0.79–1.19	0.0	3	4	1.27	0.71–2.28	77.5
Male	1	2	0.90	0.67–1.20	0.0	2	3	1.09	0.82–1.44	0.0
Breast	5	5	1.08	0.86–1.36	57.1	5	5	1.11	0.74–1.67	63.8
Cancer-free baseline	2	2	1.23	0.82–1.82	55.7	2	2	0.59	0.36–0.97	0.0
Other[b]	3	3	0.98	0.77–1.26	44.3	3	3	1.49	1.18–1.89	0.0
Ovarian	1	1	1.01	0.73–1.40	–	1	1	1.08	0.82–1.42	–
Prostate	4	4	1.02	0.88–1.18	0.0	5	5	0.94	0.66–1.32	43.4
All-cause mortality										
Cancer site										
Colorectal	2	2	1.13	0.91–1.40	8.8	2	2	1.01	0.83–1.24	0.0
Breast	3	3	1.01	0.90–1.14	0.0	3	3	1.38	1.16–1.64	0.0
Liver/pancreatic	1	1	1.29	0.37–4.47	–	1	1	3.35	0.74–15.15	–

[a]Studies were represented only once in each pooled hazard ratio estimate, except when the published article only reported subgroup results (i.e., estimates by sex). In these instances, each subgroup was treated as a different study in random-effects models

[b]Includes studies that may incorporate individuals with pre-existing cancer diagnoses in sample

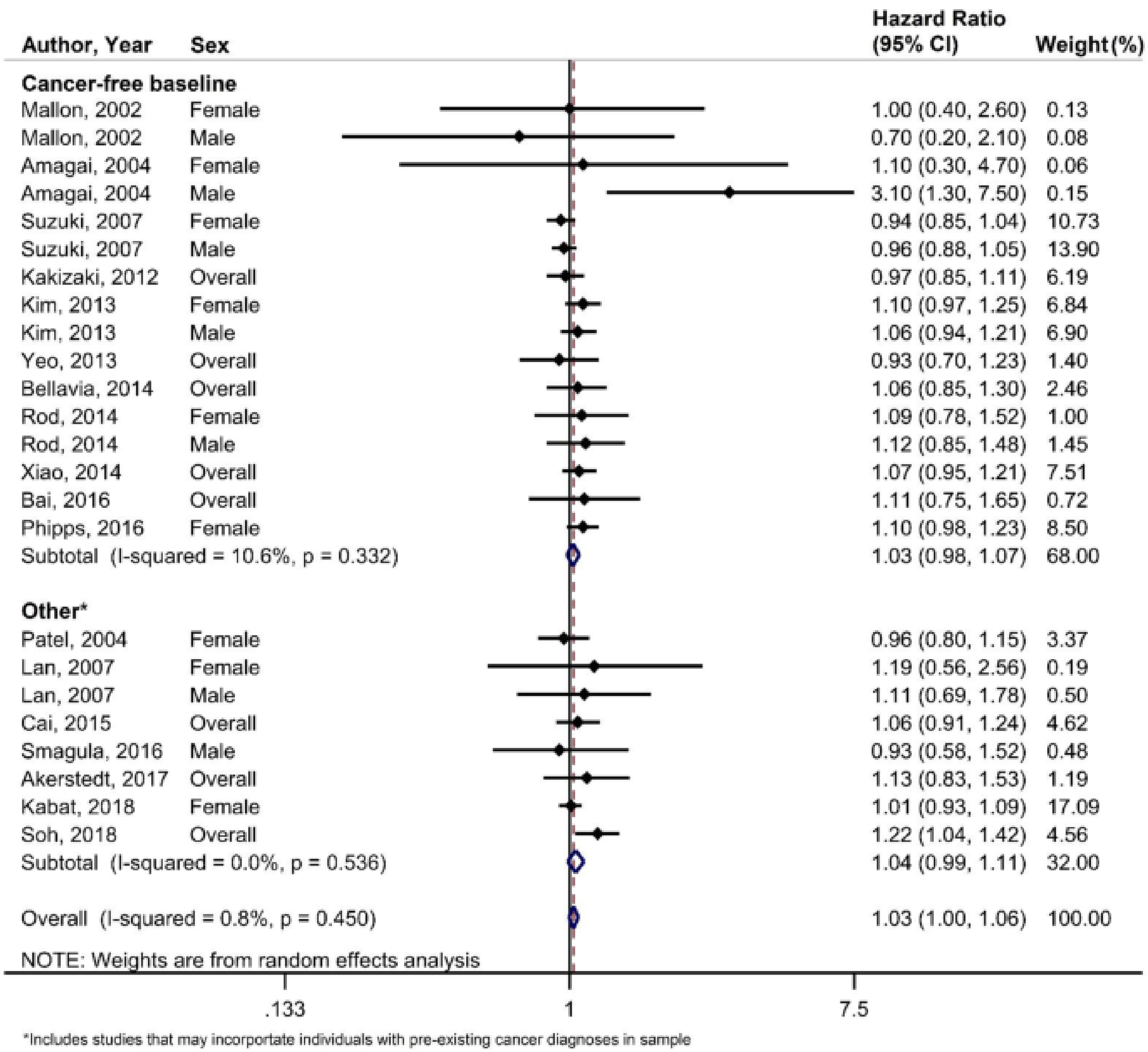


Fig. 2. Forest plot for the association of short sleep duration and all-cancer-specific mortality, stratified by sampling frame

In studies investigating all-cause mortality in colorectal, breast, or liver/pancreatic cancer survivors, there were no statistically significant associations with short sleep duration and mortality (HR = 1.13; 95% CI 0.91–1.40, HR = 1.01; 95% CI 0.90–1.14 and HR = 1.29; 95% CI 0.37–4.47, respectively).

Long sleep duration and mortality

The forest plot for all-cancer-specific mortality related to long sleep duration is shown in Fig. 3. For all-cancer-specific mortality, there was an 9% increased risk for individuals reporting the longest sleep durations compared to recommended reference ranges (HR = 1.09; 95% CI 1.04–1.13), with low evidence of heterogeneity ($I^2 = 5.4\%$). Studies that did not exclude individuals with pre-existing cancers displayed higher risk of mortality for long sleep duration compared to reference ranges than studies that were explicitly cancer-free at baseline (HRs 1.18 vs. 1.06), though results were not statistically different. When stratified by sex, all-cancer-specific mortality estimates continued to display statistically significant increased risk in both males and females (HR = 1.10; 95% CI 1.05–1.16 and HR = 1.13; 95% CI 1.03–1.23, respectively) (Table 2).

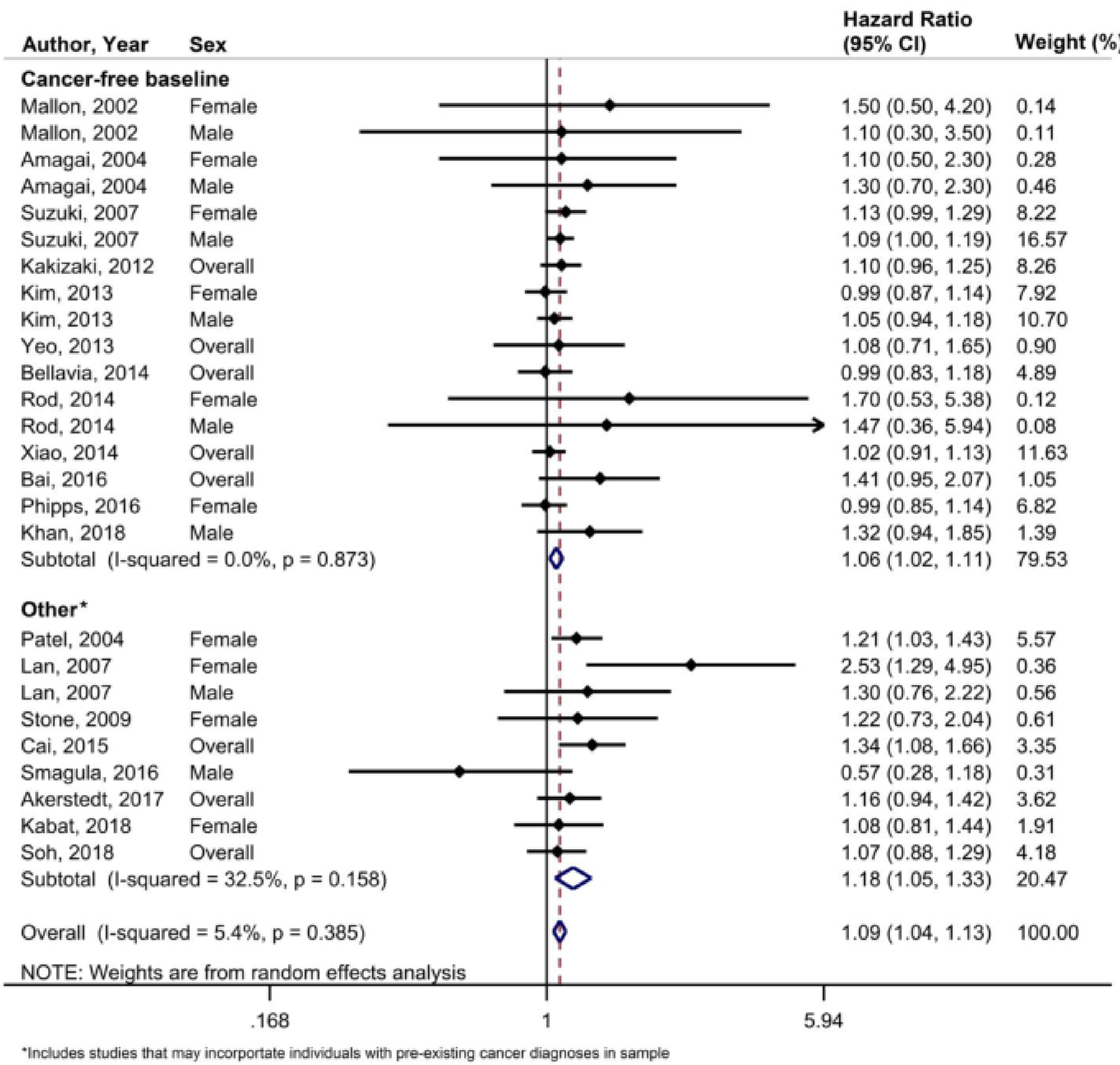


Fig. 3. Forest plot for the association of long sleep duration and all-cancer-specific mortality, stratified by sampling frame

In subgroup analyses by cancer site, there was a 65% increased risk for lung cancer (HR = 1.65; 95% CI 1.36–2.00). Further stratification of lung cancer-specific estimates by sex found that males (HR = 1.79; 95% CI 1.32–2.43) had an increased risk of mortality compared to females (HR = 1.51; 95% CI 1.18–1.93), though results were not significantly different. Colorectal, breast, ovarian, and prostate cancer sub-groups found non-statistically significant associations between cancer-specific mortality and long sleep duration with HRs of 1.12 (95% CI 0.91–1.37), 1.11 (95% CI 0.74–1.67), 1.08 (95% CI 0.82–1.42), and 0.94 (95% CI 0.66–1.32), respectively.

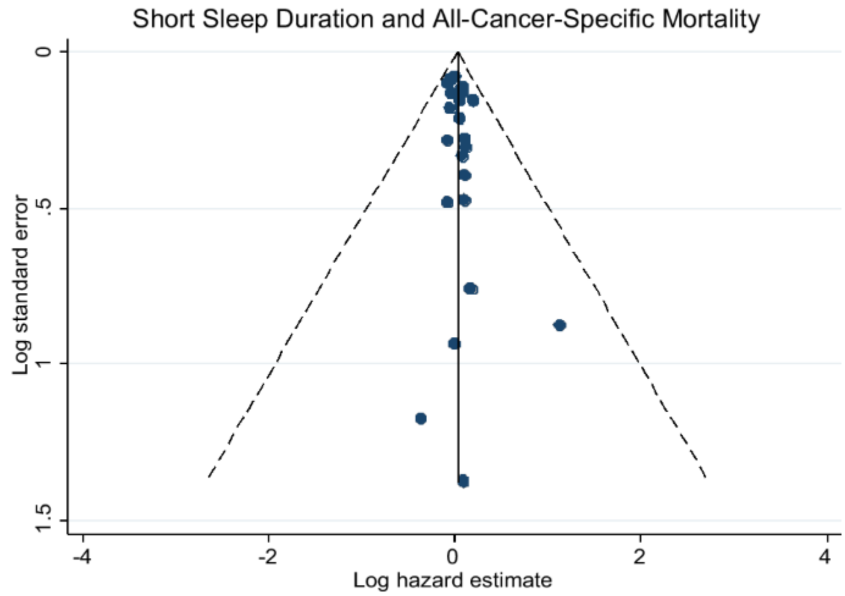
When evaluating all-cause mortality among cancer survivors, breast cancer survivors were found to have an increased risk of all-cause mortality associated with long sleep duration (HR = 1.38; 95% CI 1.16–1.64). Colorectal and liver/pancreatic cancer survivors were not found to have statistically significant increased risk of all-cause mortality with HRs of 1.01 (95% CI 0.83–1.24), and 3.35 (95% CI 0.74–15.15), respectively.

Heterogeneity assessment

When assessing heterogeneity using meta-regression modeling, sex and sampling frame were not found to a statistically significant source of heterogeneity in either short or long sleep durations by all-cancer or site-specific estimates where applicable. Heterogeneity by sex within all-cause mortality was unable to be assessed because of the limited number of studies. All included studies for all-cause mortality utilized the similar sampling frames, therefore heterogeneity assessments for these estimates were not performed.

Publication bias

Funnel plots for both short and long sleep durations in all-cancer-specific mortality are presented in Fig. 4. A visual examination of the funnel plot for short sleep duration shows a relatively symmetrical distribution of studies, with the both the Begg's test ($p = 0.99$), and the Egger's test ($p = 0.14$) indicating a lack of publication bias present. The funnel plot shows more asymmetry for long sleep duration, with fewer protective studies being published; however, the Begg's test ($p = 0.16$), and the Egger's test ($p = 0.05$) found that this asymmetry was only moderately supporting the presence of publication bias.



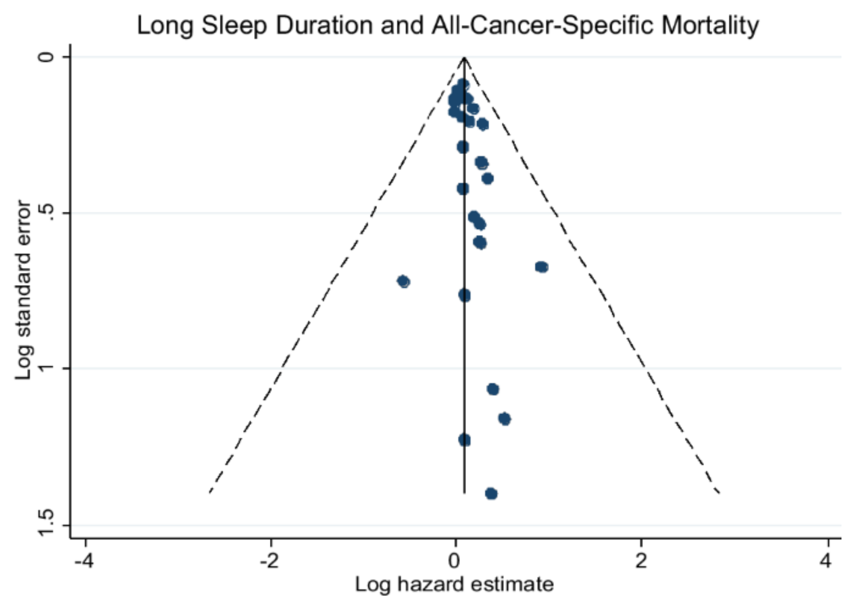


Fig. 4. Funnel plots with the log hazards ratios (*x*-axis), log standard errors (*y*-axis), and pseudo 95% confidence limits for short sleep duration (24 estimates) and long sleep duration (26 estimates) with all-cancer-specific mortality

Discussion

This systematic review and meta-analysis suggests that both short and long sleep durations are associated with an increased risk of cancer mortality. More specifically, a statistically significant 21% increased risk was found with short sleep duration and lung cancer-specific mortality. Long sleep duration was associated with a 9% increased risk of mortality from all-cancers, a 65% increased risk of lung cancer-specific mortality, and a 38% increase risk of all-cause mortality within breast cancer survivors. The discovery that some cancer sites (i.e., lung and breast) have significant associations with between sleep duration and mortality, while other sites (i.e., colorectal, prostate, ovarian and liver/pancreatic) do not suggests that these associations vary by cancer site and need to be considered separately rather than combining all-cancers together. It is also important to recognize that each cancer site has a distinct etiology, treatment regimens, side effects from treatments, and mortality rates [61]. The statistically significant finding between long sleep duration and all-cancer-specific mortality may exist because of higher proportions of lung cancer survivors included in these studies. Since the majority of the studies to date have not examined these associations by cancer site, it is not possible to conclude that there is an increased risk between long sleep duration and all-cancers. To understand these associations more fully, future studies need to examine these associations by cancer site.

Our meta-analysis confirms findings from a published meta-analysis investigating the effect of short and long duration sleep durations on all-cancer-specific mortality, whereby significant results were found for long but not short sleep duration [10]. Our meta-analysis also presents estimates separated by cancer site and sex and sampling frame sub-groups within cancer sites, which have not yet been examined in previous meta-analyses. Additionally, this meta-analysis is the first to examine all-cause mortality within cancer survivors. Five of the six included studies with these estimates were published within the last year; hence, the study of sleep duration as a modifiable lifestyle factor for all-cause mortality within cancer survivors is gaining increased recognition [16, 17, 50, 58, 60].

Lung cancer-specific mortality was associated with both short and long sleep durations. Studies investigating lung cancer mortality and sleep duration produced estimates with substantial heterogeneity for both short and long sleep durations ($I^2 = 58.4\%$ and 84.5%, respectively), suggesting that more research is needed to determine the true relation between sleep duration and lung cancer mortality. While sleep duration may not directly be the cause of mortality in this population, the comorbid conditions and side effects present within lung cancer survivors especially, have been associated with irregular sleep patterns. Some of the side effects experienced are respiratory symptoms, coughing, chest tightness, shortness of breath and have been related to poor sleep efficacy [62]. The mitigation of these comorbid conditions may help improve sleep hygiene and quality of life within this population.

More robust associations were observed between long sleep duration and our mortality outcomes, including several subgroup analyses. The exact biological mechanisms whereby long sleep duration increases mortality risk in cancer survivors are largely unknown. However, long sleep duration has been previously associated with increased cause-specific mortality [5, 7] and all-cause mortality [3, 63] within the general population, and it has been speculated that individuals who sleep longer are often affected by a worsening physical condition, comorbidities, poor pre-existing health, depression, or reflecting the process of dying [64,65,66]. Furthermore, increased time in bed coupled with poor sleep quality/frequent awakenings throughout the night may confound the sleep–mortality risk association, since many participants may report time in bed rather than actual sleep duration [67, 68]. To date, we found only one study investigating the effects of sleep quality on mortality in cancer populations [18]. Further, there are currently no studies that have investigated the joint effects of sleep duration and quality on mortality outcomes in cancer populations, suggesting that future studies are needed to investigate these associations further. The potential biological mechanisms whereby short sleep duration influences mortality are less known compared to those related to long sleep duration. In general, long sleep durations pose greater risks of mortality for the reasons previously explained; however, studies have found elevated inflammatory processes and altered metabolic processes (e.g., increased orexigenic hormones and cortisol release, altered glucoregulatory responses/insulin resistance) in short duration sleepers [69,70,71,72], which may increase mortality risk.

This study has several notable strengths. First, our literature search strategy was comprehensive and included a large number of cancer survivors from 32 studies, providing substantial power to detect even weak associations between sleep duration and mortality. Moreover, this review includes twice as many studies as a recent review on the topic, because of the broadened inclusion criteria investigating any cancer site [10]. Secondly, our study quality appraisal was rigorous and the studies included were determined to be of moderate-to-high quality. Third, minimal heterogeneity was observed for both long and short sleep duration suggesting that these studies are comparable and pooled associations reflect true associations. While various cut-off points were used to define short and long sleep durations, there was consistency overall in defining recommended sleep durations and identifying short and long sleep durations across the included studies. Finally, we conducted an extensive number of subgroup analyses by both sex and cancer site.

Several limitations should also be considered when interpreting the results of this study. First, we were unable to confirm whether or not sleep duration was affected by other underlying health conditions since not all included studies adequately controlled for the presence of comorbid sleep disorders or other comorbidities that may impact sleep duration. Second, many studies use self-reported measurements of sleep duration which may lead to exposure misclassification. Third, though sampling frame was not a statistically significant source of heterogeneity in our analyses, differences in estimates by exposure timing exist which need to be accounted for in future studies and acknowledged when comparing estimates across studies with different sampling frames. Finally, the impact of disease stage could not be assessed since few of the included studies adjusted for stage and none of the included studies presented stratified analyses by stage. Efforts to mitigate this limitation in future studies are warranted since disease stage is associated with both sleep disturbances [73] and mortality [74].

In conclusion, this review is the first to investigate the association of short and long sleep duration with cancer-specific mortality by cancer site, as well as all-cause mortality among cancer survivors. Both short and long sleep duration were associated with increased mortality, though estimates were greater for long sleep duration. Additional large-scale prospective studies are warranted to help understand this relation, especially those investigating cancer site-specific estimates since there is evidence that sleep may be a modifiable risk factor for reducing mortality risk in some cancer sites (i.e., breast and lung) but not all.

Abbreviations

CI: Confidence interval
HR: Hazard ratio
RR: Risk ratio

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